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Please provide the following references for use in examining 09/853,895

Anesthesiology (Hagerstown), (1996) Vol. 84, No. 5, pp.
1205-1214.

Journal of Neuroscience (1996), 16(23), 7407-7415

Neuroscience Research (Shannon, Ireland) (1999),
33(2), 111-118

Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1,
pp. 416. print.

Anesthesiology (2001), 94(6), 1010-1015

NeuroReport (2001), 12(15), 3251-3255

European Journal of Pharmacology, (March 31, 2000) Vol.
392, No. 3, pp. 141-145.

Thank-you!

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158.17

INVOLVEMENT OF P2X RECEPTOR SENSITIVITY IN SENSORY NEURONS DISPLAYING ECTOPIC DISCHARGES AFTER SPINAL NERVE INJURY. J. Zhou¹, K. Chung¹ and J.M. Chung¹. *1. Marine Biomed Inst and Dept of Anat & Neurosci, Univ Texas Med Br, Galveston, TX, USA*. It is known that P2X purinoceptors are expressed in the cell bodies of many sensory neurons. After peripheral nerve injury, some axotomized afferent neurons develop ongoing discharges that originate in the dorsal root ganglion (DRG). In the present study, we attempted to determine whether or not purinergic sensitivity develops in injured sensory neurons displaying ectopic discharges. The L4 and L5 spinal nerve were ligated in male Sprague-Dawley rats. At various times after spinal nerve injury, the L4 and L5 dorsal root ganglia with attached dorsal roots and spinal nerves were removed and ectopic discharges were recorded from teased dorsal root fascicles in an in vitro set-up. Adenosine 5'-triphosphate (ATP) and α,β -methylene ATP (mATP) sensitivity developed at 13 hours after the ligation and was maintained at least 3 weeks. Of the chronically axotomized DRG neurons displaying ectopic discharges, 75.6% and 60.2% showed enhanced activity to application of ATP (1 mM) and mATP (100 μ M), respectively. In contrast, only one of 34 DRG neurons acutely isolated from normal rats responded to either mATP or ATP. In most of the tested units, mATP-induced enhancements of ectopic discharges were blocked by a non-specific P2X receptor antagonist, such as PPADS or suramin. The data suggests that purinergic sensitivity develops in DRG neurons displaying ectopic discharges after chronic axotomy and that this purinergic sensitivity is likely mediated by P2X purinoceptors. Supported by NIH Grants NS 31680, NS 11255 and NS 35057.

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PAIN: DEVELOPMENTAL ASPECTS—GROWTH FACTORS AND GENDER DIFFERENCES

159.1

EXPRESSION AND DEVELOPMENTAL CHANGES OF PSD-95 AND PSD-93 IN RAT SPINAL CORD. Y.X. Tan¹, C.F. Levine¹, M. Fang¹, J.A. Gonzalez¹, F. Tao¹, R.L. Huganir², D.S. Bredt³ and R.A. Johns¹. *1. 1Dept Anesthesiology, Johns Hopkins Univ Sch Med, Baltimore, MD, USA, 2. 2Dept Neuroscience, Johns Hopkins Univ Sch Med, Baltimore, MD, USA, 3. 3Dept Physiology, Univ of California, San Francisco, CA, USA.*

We have demonstrated that PSD-95 is critical for NMDA receptor-mediated spinal hyperalgesia. To further provide morphological support, the present work examined the expression and developmental changes of PSD-95 and its family member, PSD-93, in the spinal cord. Immunoblotting analysis showed that PSD-95 and PSD-93 but not SAP97 were enriched in the spinal cord and other brain regions. PSD-95 and its family members were not detected in the dorsal root ganglia. Immunocytochemistry revealed that PSD-95 was distributed mainly in lamina I of the spinal cord, while PSD-93 was concentrated in both laminae I and II. During postnatal development in the spinal cord, these two proteins exhibited distinct changes in expression. PSD-95 was strongly expressed before postnatal day 10 and showed a substantial decrease by 6 months. However, PSD-93 expression was at a low level prior to postnatal day 5, reached a peak at postnatal day 20 and was slightly reduced by 6 months. Immunoprecipitation experiments demonstrated that both PSD-95 and PSD-93 in the spinal cord interacted with NMDA receptors. The area-specific expression and distribution of PSD-95 and PSD-93 suggest that PSD-95 and PSD-93 are important in mechanisms of spinal nociceptive processing. Moreover, distinct distribution and developmental changes in PSD-95/SAP90 and PSD-93 expression indicate that they might have specific functions that are critical to synaptic development and signal transduction in the spinal cord. Supported by NIH grants RO1 GM49111 and RO1 HL39706.

159.2

PRENATAL STRESS SUPPRESSES THE SYMPATHO-ADRENAL RESPONSE AND INCREASES PAIN BEHAVIORS IN THE FORMALIN TEST IN DEVELOPING RATS. I.P. Butkevich¹ and V.A. Mikhailenko¹. *1. Lab Ontogeny Higher Nervous Activity, Russian Academy Sci, St Petersburg 199034, Russian Federation.*

Effects of prenatal stress (immobilization in the last week of pregnancy) on biphasic nociceptive behaviors in the formalin test (2.5%, 10 μ l, s.c. formalin injection into a hind paw) and on the sympatho-adrenal response to formalin-induced pain were studied in 25-day-old rats. In each rat total urinary adrenalin, norepinephrine and dopamine excretion during a 0-24 h period both before and after formalin-induced pain was investigated. Prenatally stressed rats showed a robust increase in flexing+shaking behaviors during the second phase of the formalin test. Formalin-induced pain evoked in all rats the increase of the urinary adrenalin and norepinephrine but not of dopamine excretion. In prenatally stressed rats the increase of catecholamine excretion after nociceptive responses was pronounced to a lesser degree as compared to non stressed rats. Prenatally non stressed rats showed sex dimorphism in the urinary adrenalin and norepinephrine excretion whereas stressed rats only in norepinephrine one. In males compared with females the level of the catecholamine excretion was higher. Thus, in 25-day-old rat pups the consequences of prenatal stress manifested themselves in the enhancement of pain sensitivity and in decline of the reaction of sympatho-adrenal system in response to formalin-induced pain.

159.3

GENDER DIFFERENCES IN HYPERALGESIC EFFECT OF MORPHINE IN RATS. E.P. Wala¹, X. Jing¹ and J.R. Holtman, Jr.¹. *1. Anesthesiology, University of Kentucky, Lexington, KY, USA.*

Several laboratories (including ours) have showed a greater analgesic responsiveness to morphine in male than in female rats. Although hormonal and pharmacokinetic factors have been considered, the mechanism of action is not clear. As part of our studies on gender-specific actions of analgesics we found that low dose of morphine paradoxically produces hyperalgesia (enhanced nociception). The present study characterized this hyperalgesic response and possible sexual dimorphism in the rat. Responses to nociceptive thermal stimuli (tail-flick test) were tested in age-matched, Sprague-Dawley male and female rats (~90 days old, 350 and 250g, respectively). Rats (10/sex) were exposed to different intensities of radiant heat (Latin square design; 10min intervals). Tail flick latency (TFL) linearly decreased (15-2.5sec) with increasing intensity (0.5-2.5) of heat ($p < 0.001$). Reactivity was not related to gender. Rats (20/sex) were randomly injected IP at weekly intervals with morphine (0.002-0.2mg/kg) or saline prior to exposure to the low intensity heat (baseline TFL ~10sec; cutoff time=20sec). TFL was assessed prior to and 5-120 min after injection. Regardless of gender, saline caused a weak hyperalgesia. Morphine (0.2mg/kg) had a negligible effect in either gender. Morphine (0.02 and 0.002mg/kg) produced a marked hyperalgesia in female whereas this effect was significantly lesser in male rats ($p < 0.05$). Areas under the curves were reciprocally related to dose of morphine in female ($p < 0.0001$) but not in male rats. Data revealed that the nociceptive-enhancing effect of a low dose of morphine is greater in female than in male rats. Supported by University of Ky Anesthesiology Dept.

159.4

EXCISIONAL SKIN WOUNDS INCREASE ACTIVIN IN SKIN AND A NOCICEPTIVE PEPTIDE IN SENSORY GANGLIA. B.A. Cruise¹, K.J. Dinsio¹ and A.K. Hall¹. *1. Neurosciences, Case Western Reserve Univ, Cleveland, OH, USA.*

Activin can regulate sensory neuron differentiation during development, but its role in the adult nervous system is unknown. While activin is expressed in embryonic skin and is proposed to alter sensory neuropeptides, in adult skin, activin is downregulated to very low levels. Two days after an excisional skin wound, however, activin protein expression in adult skin adjacent to the wound increased. By contrast, the expression of other TGF-beta family members, such as bone morphogenetic proteins-2, -4, and -6, decreased in skin following the wound. The skin is innervated by sensory neurons, some of which contain nociceptive peptides like calcitonin gene-related peptide (CGRP). In response to the excisional skin wound, the number of neurons expressing CGRP increased in the sensory neurons that project to the wound. Nerve growth factor (NGF) levels in the skin have been shown to increase following inflammation, and NGF levels in skin also increased following an excisional wound. The upregulation of activin does not affect NGF levels in cultured skin cells, or vice versa, suggesting these ligands are independently regulated. Since activin has been shown to increase sensory neuropeptide expression during development, and its expression is upregulated in the adult after a skin wound when sensory neuropeptides also increase, this skin protein may regulate the change in nociceptive peptides in the DRG following a skin injury. Supported by National Institutes of Health NS 39316.